Name of journal: World Journal of Hepatology
Manuscript NO.: 20636
Column: Editorial
Title: Wilson's Disease: What have we learned?
Authors: Kryssia I Rodriguez-Castro, Francisco J Hevia-Urrutia and Giacomo C Sturniolo
Correspondence to: Dr. Kryssia I. Rodriguez-Castro, MD, PhD. Gastroenterology Policlinico Abano Terme Piazza Cristoforo Colombo 1. 35031 Abano Terme. Italy
Telephone: +39 3336167592 Email: kryssiarodriguez@yahoo.com
Reviewer code:
First decision:
Scientific editor: Fang-Fang Ji

Point-by-point response to Reviewers

Reviewer 00053746

The Authors wish to thank the Reviewer for the thoughtful comments and suggestions, that have all been incorporated and have improved the quality of the manuscript.

It has been clarified that the test proposed by some groups regarding the 6-hour challenge test with penicillamine is not a standard method and is not reccommended as a routine technique. The following statement has been added: This test has not yet been universally validated yet, however, and has not been standardized for routine diagnosis, but rather represents a valid tool under certain circumstances, especially in patients with acute on chronic presentation with rapid clinical deterioration. Regarding genetic testing, the following sentence has been corrected, as suggested, as follows: Genetic testing might prove to be very useful, and molecular techniques allow for a rapid diagnosis in a substantial part of patients with prevalent mutations. Moreover, the following sentence was added: Furthermore, genetic testing is especially useful in screening relatives of the index patient, upon determination of his/her mutant. As suggested, it has been clarified that the therapeutic strategy of combination zinc plus penicillamine therapy is not standardized.

Reviewer 00502871

The Authors wish to thank the Reviewer for the thoughtful comments and suggestions, that have all been incorporated and have improved the quality of the manuscript.

Reviewer 02444981

The Authors wish to thank the Reviewer for the thoughtful comments and suggestions, that have all been incorporated and have improved the quality of the manuscript.

According to the Reviewer's suggestion, a statement has been made in the introduction (which is echoed in the "Treatment" section regarding the concept of orphan drugs) regarding the lack of solidity behind most interventions, which have lacked the rigorous testing of randomized controlled trials. The following sentence has been included: Much of the knowledge that has accumulated in the decades following the first description of the disease, as well as the mainstays of treatment, derive greatly from experts' opinions and some from anecdotal experiences, and not on adequately designed randomized comparative studies. As suggested by the reviewer, the title was changed to: "Wilson's Disease: A review of what we have learned". With this new title, the idea that the authors want to convey is that after a century of the recognition of the disease, the diagnostic and therapeutic armamentarium has grown very slowly, as our understanding of mechanisms of disease and of pharmacological agents used, partly due to the rare nature of the disease and the resulting lack of interest from the pharmaceutical industry. Thus, the manuscript aims at guiding the reader through an overview of this disease. The keywords have also been modified accordingly. The new paradigm regarding free copper toxicity vs the old paradigm regarding copper accumulation has been included. The following sentences have been incorporated into the manuscript: It is now known that it is not the accumulation of copper itself what is deleterious to the organism, but rather free copper in the blood, which determines copper intoxication, as opposed to ceruloplasmin-bound copper. Thus, the old

paradigm of eliminating copper stores as the therapeutic objective has given way to the concept of normalizing free copper concentrations in the bloodstream. Moreover, in the section on zinc therapy, the following sentence has been added: As the deleterious effect of copper is associated with its free form in blood, induction of metallothionein and its binding of free copper by zinc results in an efficacious therapy, achieving normalization of free copper levels. Line 6 in the introduction has been corrected, and it now reads: Consequences of this defect are the impaired copper metabolism and consequent copper intoxication. The section on Pencillamine has been divided into 3 paragraphs, as suggested (Pages 5-6). The statement regarding penicillamine as the agent of choice has been corrected, and it has been stated that it is widely employed but not as a result of comparative tests; the new sentence reads as follows: Although initial worsening of neurologic symptoms may occur in 10-50% of patients[53,70], it is widely used due to its low cost and considerable efficacy, although no comparative data exist to support its superiority as opposed to zinc therapy.

In the section on Trientine, the sentence which refers to the clinical profile of trientine has been modified according to the reviewer's suggestion, emphasizing that no actual controlled study has demonstrated its safety profile, but rather this information derives from uncontrolled studies. The new sentence reads as follows: Although its elevated cost might hamper its use as an initial medication, and although clinical information available is limited only to uncontrolled studies, this agent possesses a good safety profile and is efficacious, offering the possibility of use as alternative to other pharmacological agents or as initial therapy, even in cases of decompensated liver disease. Moreover, the phrase stating that this agent was "seemingly" associated with a lesser frequency of neurological worsening has been complemented by the following sentence: Cases of neurotoxicity have been reported[84], however, and a clinical trial found that trientine led to initial neurological deterioration in approximately 26% of treated patients. The first sentence on the "Zinc" section was corrected as follows: Initially its chloride salt, followed by its sulfate salt, zinc was first used in the early 1960s to treat WD but was kept unrecognized until 1978. Reference 60 was deleted, as suggested. Moreover, it was clarified that zinc acetate is considered to have better gastric tolerance, but that all zinc salts have demonstrated similar efficacy. The new sentence reads as follows: Zinc acetate is regarded to have a better

gastric tolerance. However, in terms of efficacy, there is no difference between zinc salts. The reference was modified accordingly.

Regarding liver transplantation, it is clear that this operation is indicated only as a life-saving measure where otherwise death would be the case, as in fulminant hepatic failure or in advanced stages of cirrhosis, which are seen mostly in patients with delayed diagnosis whose disease has progressed without treatment. The sentence is correct in the sense that liver transplantation does correct the metabolic derangement and the patient does not need specific therapy for WD after transplantation. However, it is by no means intended to be the primary therapy, since effective pharmacological management can be readily achieved, providing prompt diagnosis is made and adequate compliance is ensured. The following sentence has been added: With the availability of effective treatment, liver transplantation is clearly not indicated to treat the metabolic defect, but rather as a life-saving procedure in cases of advanced cirrhosis or fulminant hepatic failure.

The studies in which neurological improvement has been shown after liver transplantation have been added. The following sentence has also been included, clarifying that liver transplantation for the sole neurological involvement is not indicated: Moreover, liver transplantation for sole neuropsychiatric disease is currently not recommended.

Regarding liver transplantation, the references have been added. (page 10). Evidence that RWPI predicts mortality without liver transplantation are included in the manuscript (please see references Petrasek Liver Transplantation 2007 and Nazer Gut 1986.

The reviewer's comment on birth defects in pregnancy regarding that "even few cases are enough to cone" does not take into consideration that birth defects affect 3% of all deliveries, and the low number of birth defects in patients with Wilson Disease cannot be attributed to the disease or to the treatment, since it has not been quantified to be superior to that of the general population.

Reviewer 00051398

The Authors wish to thank the Reviewer for the thoughtful comments and suggestions, that have all been incorporated and have improved the quality of the manuscript.

The sentence has been modified to include the study describing the Asn 1270Ser mutation in the Lebanese population. The sentence now reads as follows: The country with the highest incidence in the world, however, is Costa Rica (4.9/100.000 inhabitants; see below section on perspectives from a high-incidence country), possibly due to elevated degree of consanguinity and a possible founder effect, the most frequent mutant being Asn 1270 Ser[16,17], previously described only in Sicilian, Lebanese and Turkish populations.

The reviewer is gently invited to note the second paragraph on page 11, which states the possible consequences of long-term therapy, including anemia due to failed iron mobilization.